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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/413,109	10/06/99	ZHANG W	INRP;087/SHS

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GINA N. SHISHIMA, ESQ.
FULBRIGHT & JAWORSKI
600 CONGRESS AVENUE
SUITE 1900
AUSTIN TX 78701

EXAMINER	
GUZO,D	
ART UNIT	PAPER NUMBER
1636	17

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/413,109	Applicant(s) ZHANG ET AL.	
	Examiner David Guzo	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-97* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *15* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 79-97 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating cancers wherein the cancer cells lack a functional p53 gene, said method comprising direct administration of recombinant adenovirus comprising a DNA sequence encoding (and expressing) wild-type p53 to the tumor , does not reasonably provide enablement for treating any cancers comprising using an adenovirus comprising the p53 gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with the information known in the art without undue experimentation (United States v. Teletronics Inc. 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is needed is not based upon a single factor, but rather a conclusion reached by weighing many factors. These factors are outlined in *Ex parte Forman* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and they include the following:

1) Unpredictability of the art. The gene therapy art is extremely unpredictable. The ability of a given adenoviral vector to deliver and express a p53 gene in cancer cells which lack a functional p53 gene and inhibit the growth of said cells provides no teaching on whether said vector will inhibit or stop the growth of cancers which are the result of other mutations unrelated to p53 gene abnormalities. Indeed, given the vast variety of oncogenes, tumor suppressors genes and other genetic phenomena involved in tumorigenesis, it is totally unpredictable whether the instant adenoviral; vector can prevent growth of human cancer cells which are the result of mutations in tumor suppressor genes unrelated to p53 or the result of activation of oncogenes, etc. Applicants have presented no evidence that the instant vectors can prevent growth of cancer cells which have a normal p53 gene. Furthermore, with regard to the unpredictable nature of gene therapy in general, applicants are encouraged to review the following citations (See Fox, Nature Biotechnology, 2000, Vol. 18, pp. 143-144; Kmiec, American Scientist, 1999, Vol. 87, pp. 240-147; Anderson, Nature, 1998, Vol. 392, pp. 25-30; Verma et al., Nature, 1997, Vol. 389, pp. 239-242; Ross et al., Human Gene Therapy, 1996, Vol. 7, pp. 1781-1790, etc.). Given the unpredictable behavior of gene therapy vectors *in vivo* and given the many failures in gene therapy, it is impossible to predict, *a priori*, the *in vivo* characteristics of gene therapy vectors and whether said vectors will have any therapeutic effects in patients.

Specifically, with regard to recombinant adenoviral vectors, recent human studies have revealed the complex, unpredictable behavior of these vectors in patients. Fox (cited above) notes that the clinical use of adenoviral vectors is complicated by unpredictable delivery of the

transgenes, by problems in determining therapeutic vs. toxic (or fatal) doses of the vector, by differences in how the adenoviral vectors behave in humans compared to behavior in animal models, etc. Also, with regard to gene therapy for cancer, Gomez-Navarro et al. (Euro. J. Cancer, 1999, Vol. 35, No. 6, pp. 867-885) note that significant obstacles to mutation compensation remain to be solved before this methodology can be successfully used to treat cancer. These obstacles involve the remarkably heterogeneous nature of the patterns of expression of relevant oncogenes in many human tumors, the fact that some mutated genes exhibit a transdominant effect which cannot be overcome by merely supplying the wild-type gene, the poor level of understanding of the tumor-supportive micro-environment and of multicellular tumor phenomena which can overcome any therapeutic effect of the vector, etc.

With regard to the methods of delivery of the vector to the cancer, Gomez-Navarro et al. note that as of 1999: "To date, *in vivo* cancer gene therapy strategies have been restricted to treatment of compartmentalized tumours in an attempt to achieve high local vector concentrations and relatively efficient tumour transduction." (P. 877). Gomez-Navarro et al. also note current vectors are not suitable for intravenous or other systemic methods of delivery to cancers.

2) State of the art. The state of the art at the time of applicants' invention was nil with no examples of successful treatment of human cancers using adenoviral (or any other) vectors.

3) Amount of guidance provided by applicants. Applicants provide no guidance on use of the instant vector to treat human cancers which arise from genetic phenomena other than mutations in

p53. The skilled artisan would be left to attempt trial and error experimentation in order to try to use the instant vector to treat cancers other than those arising from mutations in p53.

4) Number of working examples. Applicants present no working examples of treatment of humans cancers arising from genetic phenomena other than mutations in p53.

5) Scope of the invention. The invention is broad with the claims reading on use of any adenoviral vector comprising the p53 gene inserted at any genomic location and under the control of any promoter to treat any cancer in humans.

6) Nature of the invention. The invention involves one of the most complex and unpredictable aspects of molecular biology/medicine; gene therapy using recombinant viral (adenoviral) vectors.

7) Level of skill in the art. The level of skill in the gene therapy art is high; however, as noted by some of the most prominent gene therapy researchers (i.e. Gomez-Navarro et al., W. French Anderson, Verma, etc.), the level of unpredictability in this poorly developed art is high.

Given the above analysis of the factors which the courts have determined are critical in ascertaining whether a claimed invention is enabled, it must be considered that the skilled artisan would have had to have conducted undue and excessive experimentation in order to practice the claimed invention.

2. Claims 22-78 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The grounds for rejection of these claims are essentially as given above in the scope rejection of claims 79-97 and will not be repeated here. It is again noted that Gomez-Navarro et al. (1999) indicate that *in vivo* cancer gene therapy strategies involve direct administration of the vectors to compartmentalized tumours and that present vectors are inadequate for delivery intravenously or by other systemic methods. Applicants present no guidance on how the skilled artisan would overcome these art recognized obstacles to practicing successful gene therapy.

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 22-97 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 9-13, 22-52 and 56-72 of copending Application No. 08/459,713 (hereafter the '713 application). Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant

application and the 713 application recite the same methods for treating human cancer patients comprising administering pharmaceutical compositions comprising adenoviral vectors containing the p53 gene. The claims in the '713 application differ in that they recite adenoviral vectors comprising expression cassettes for expression of the p53 gene (i.e. use of the CMV IE1 promoter, SV40 early polyA signal) wherein said expression cassettes are encompassed within the claims in the instant application, involve standard regulatory elements essential for gene expression, were disclosed in the '713 application and could have been claimed in the '713 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

5. Claims 22-97 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 30-35 of copending Application No. 08/626,678 (hereafter the '678 application). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in the '678 application recite pharmaceutical compositions comprising recombinant adenoviral vectors capable of expressing the p53 gene, wherein said pharmaceutical compositions are designed to be administered to humans for treatment of cancer (as per the instant claims). It would have been obvious to the ordinary skilled artisan to use the pharmaceutical compositions claimed in the '678 application in methods of treating cancer since these adenoviral vectors are specifically designed

to express a tumor suppressor gene (p53) which inhibit tumorigenicity or cause the death of cancer cells. With regard to the expression cassettes used to drive expression of the p53 gene in the adenoviral vectors, said expression cassettes are encompassed within the claims in the instant application and represent the standard, essential regulatory elements necessary for gene expression, were disclosed in the '678 application and could have been claimed in the '678 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

In view of the new grounds of rejection under 35 USC 112, 1st paragraph, applicants arguments are moot. With regard to the outstanding Double Patenting rejections, applicants indicate that they will respond in due course.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo whose telephone number is (703) 308-1906. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Robert Schwartzman, can be reached on (703) 308-7307. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding or relating to attachments to this Office Action should be directed to Patent Analyst Zeta Adams whose telephone number is (703) 305-3291.

David Guzo
August 27, 2001

DAVID GUZO
PRIMARY EXAMINER